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Implications of Pharmacokinetic Modeling in Risk Assessment Analysis

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Physiologic pharmacokinetic models are a useful interface between exposure models and risk assessment models by providing a means to estimate tissue concentrations of reactive chemical species at the site of action. The models utilize numerous parameters that can be characterized as anatomical, such as body size or tissue volume; physiological, such as tissue blood perfusion rates, clearances, and metabolism; thermodynamic, such as partition coefficients; and transport, such as membrane permeabilities. The models provide a format to investigate how these parameters can influence the disposition of chemicals throughout the body, which is an important consideration in interpreting toxicity studies. Physiologic models can take into account nonlinear effects related to clearance, metabolism, or transport. They allow for extrapolation of tissue concentration from high dose to low dose experiments and from species to species and can account for temporal variations in dose.

Introduction

The ever-increasing distribution of anthropogenic chemicals into our environment requires more sophisticated methods for estimating the risks posed to populations exposed to these chemicals. On one hand, procedures are being developed for determining the magnitude of ambient exposure levels and body burdens of these materials, while on the other hand, mathematical models are being derived to calculate estimates of the risks of cancer or death after such exposure. The former analysis involves exposure models, and the latter analysis refers to risk assessment models. This paper describes the concepts of a pharmacokinetic model and illustrates how such models can be a beneficial interface between the exposure models and the risk assessment models to improve and make more reliable quantitative estimates of risk. The fundamental concepts that form the basis of pharmacokinetic models will be briefly described in this paper, and a discussion of the various parameters that these models require will be given. Through the application of pharmacokinetic models, insight can be gained into the mechanisms by which physiologic processes such as blood flow, membrane permeability, binding, metabolism, etc., affect the response of an organism after exposure to toxic agents by examining how these parameters influence the disposition of the agents. Figure 1 depicts, schematically, the interrelationship of the exposure, risk assessment, and pharmacokinetic models. Risk assessment models are designed to give some estimate of response after exposure to some dose. The environment is responsible for providing the exposure or dose to the organ or organism that is represented by the pharmacokinetic model. It is possible to circumvent the pharmacokinetic model and derive relationships directly between response and ambient exposure. However, recent research activity in this area (*1–3*) has proposed a more rational and fruitful approach that attempts to correlate response of an organism with the tissue concentration of a reactive chemical species such as a metabolite. As a further step, some researchers propose a response correlation with the concentration of a particular intracellular element at the site of action, such as DNA adduct (*4*). In any event, the pharmacokinetic model lends itself very readily to making estimates or predictions of specific, local, effective concentrations or effective doses, as labeled in Figure 1.

Biological Model

Figure 1 shows a hypothetical biological model in a target organ within our pharmacokinetic model. The biological model is further detailed in Figure 2 and represents a modified version of one proposed by Hoel et al. (*4*), which follows from suggestions of Gehring and Blau (*1*) and Gillette (*5*). Ch represents the parent chemical of interest, e.g., PCB, kepone, dioxin, etc., at some concentration within the body resulting from exposure by various possible routes such as ingestion, absorption, or inhalation. RM is a reactive metabolic intermediate that derives from Ch. CBG is a covalently bound, genetically active species. For example, Anderson et al. (*3*) propose that for vinyl chloride the CBG can be represented by a DNA adduct of a vinyl chloride metabolite

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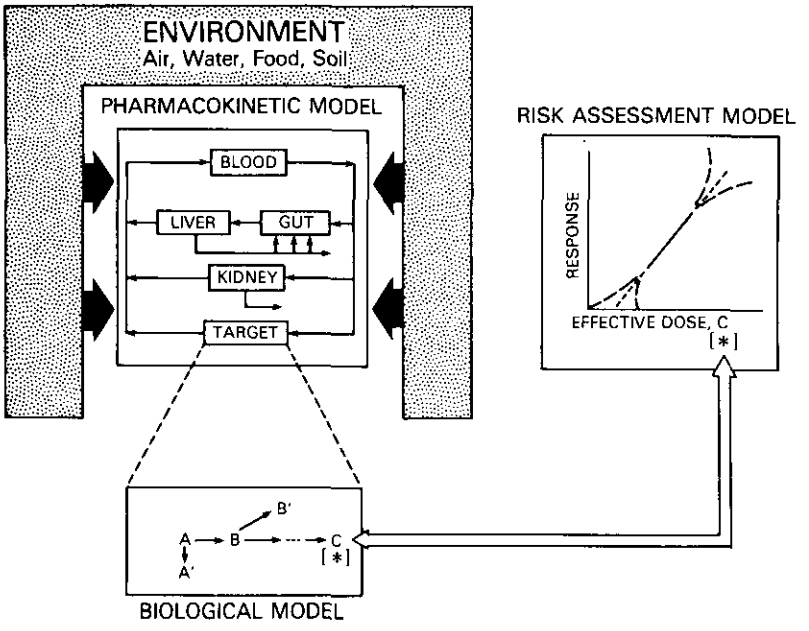

FIGURE 1. Interrelationship between exposure determination and risk assessment models using pharmacokinetic and biological models.

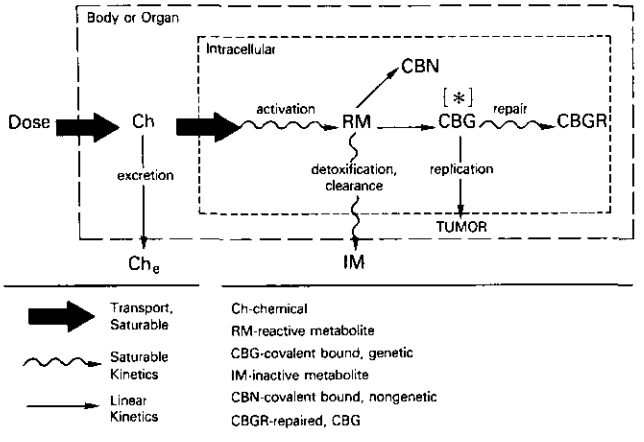

FIGURE 2. Diagram of a simple biological model for the metabolic fate of some carcinogens. [*] Indicates a genetically active species.

which represents initial genetic damage and eventually can cause tumor growth (liver angiosarcomas). Cellular processes may repair the altered material, for example, by elimination of altered bases from DNA, yielding the component labeled CBGR. This process is likely to be enzymatic. The reactive metabolite may also interact with nongenetic material in the cell such as protein, represented by CBN. If CBG is not repaired, it may cause heritable genetic transformation of a cell, which through promotional stages can propagate into a tumor. The reactive metabolite, can be detoxified, for example by the liver, and also cleared from the body. Not all of these kinetic processes are linear. Some are enzymatic and therefore follow more complex kinetics and are saturable. The saturable kinetics proposed by this model are shown in Figure 2.

In modifying the biological model as originally proposed by Hoel (*4*), some additional pharmacokinetic concepts have been added that involve transport phenomena as shown in Figure 2. These include blood flow by the circulatory system, diffusion across cell membranes, and elimination mechanisms. These processes will be discussed later to show their importance and relevance to the proposed biological model and to the overall matter of risk assessment. Most toxicity studies, such as bioassays, are done at reasonably high doses in order to elicit an observable response (*6*), such as initiation of a tumor or death in an experimental animal. However, actual exposures of interest from an environmental perspective usually occur at much lower doses. One objective of risk estimation is to extrapolate the high dose experiments to predictions of risk at low doses, but such extrapolations can be misleading if certain pharmacokinetic events are not taken into consideration. The possible consequences of the linear and nonlinear events depicted in Figure 2 on the outcome of dose-response prediction will be illustrated. We will assume, as suggested by previous literature (*4*), that the response to exposure can be directly correlated with the concentration of a reactive species, namely the CBG in Figure 2. Figure 3 illustrates several interrelationships between the applied dose and the CBG concentration or response for various kinetic or transport conditions.

Consider the simplest case in which all the transport and kinetic mechanisms depicted in Figure 2 are linear. The dose-response relationship for such a case is illustrated in Figure 3*A*, which shows that linearity is maintained at low and at high doses. Therefore, a linear extrapolation of response data from the high dose region, where most data are actually collected, to the low dose region would allow prediction of the low dose re-

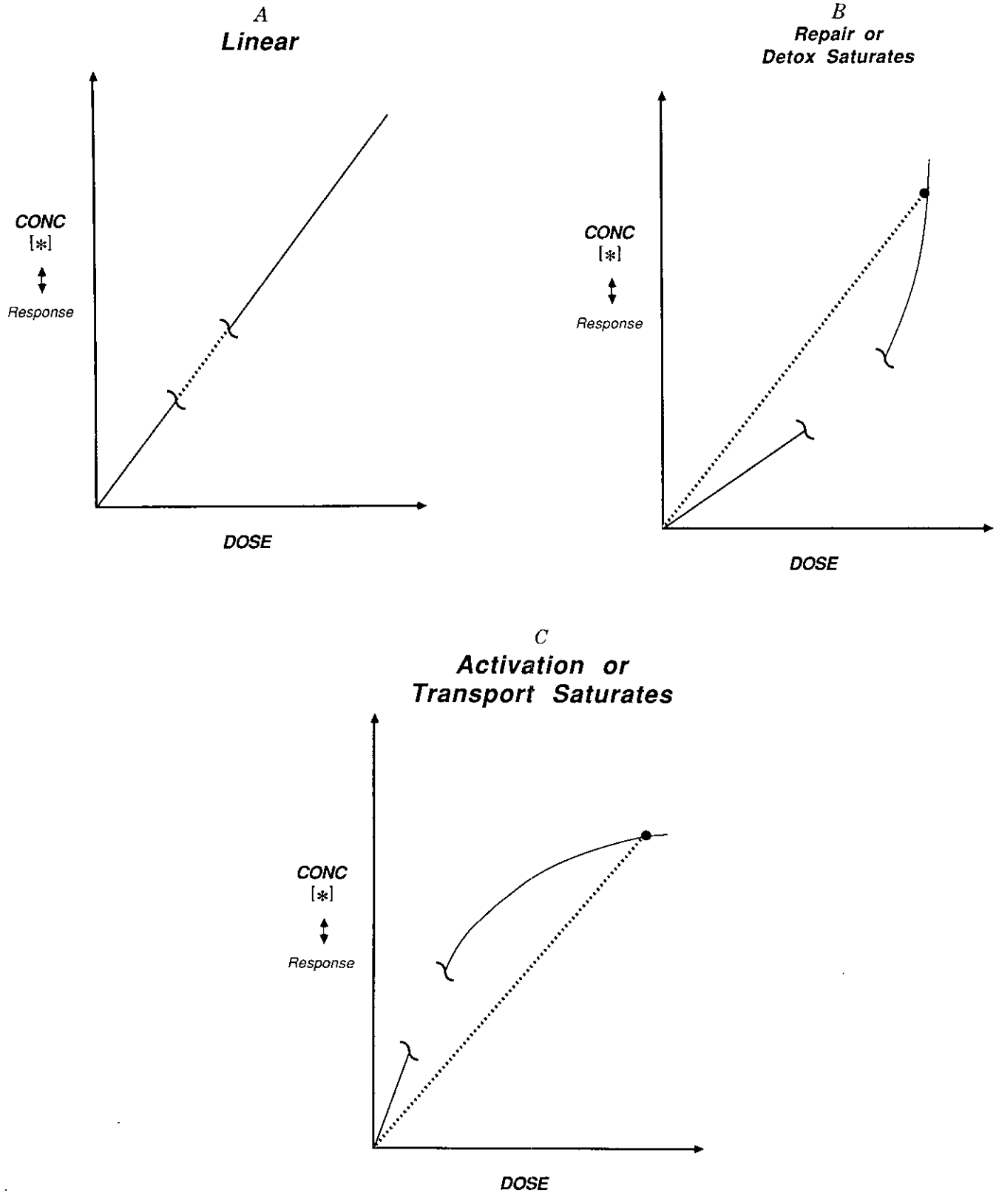

FIGURE 3. Possible relations between administered dose and concentrations of CBG [*] in Fig. 2 as a prediction of response to an exposed carcinogen. Dashed lines indicate linear extrapolation. (*A*) Represents linear kinetics; (*B*) represents saturation of the repair or detoxification steps in Fig. 2; (*C*) represents saturation of the activation or transport steps in Fig. 2.

sponse. Suppose, however, that the repair or detoxification steps of the biological model in Figure 2 were to saturate at high applied doses. The CBG concentration would increase rapidly with dose, as shown in the high dose region in Figure 3*B*. Now, linear extrapolation from a high dose experiment to zero dose would fall above the actual low dose response curve, and would overestimate the response at low doses. Conversely, if the activation step or if transport processes depicted in Figure 2 were to saturate, then the concentration of the CBG species would plateau as applied dose increased, as shown in Figure 3*C*, and linear extrapolation from a high dose experiment would underpredict actual response at low doses. The important conclusion to make from these figures is that some biochemical species, such as a DNA adduct (CBG), are better measures of effective dose for extrapolation than administered dose or exposure levels, and that it is within the realm of our physiologic pharmacokinetic modeling techniques to be able to predict the effective concentration of toxic agent from the administered dose by taking into account linear and nonlinear physiological and anatomical mechanisms.

Pharmacokinetic Model

With this background in mind, a discussion of physiologic pharmacokinetic models follows, with a few examples to illustrate how some pharmacokinetic events are relevant to toxicity. Pharmacokinetic models consist of numerous parameters such as blood flow, membrane permeability, clearance, etc., which represent actual physiological functions that influence the distribution and disposition of chemicals in the body, thereby influencing the concentration of CBG.

The mathematical bases of these models involve principles that generally apply to any chemical agent in the body, whether it is an anticancer drug for treatment or a xenobiotic that causes toxicity. An example of a pharmacokinetic system is the model for PCB distribution (*7*), shown schematically in Figure 4. The system is composed of various compartments that are linked together by a flow network, namely the circulatory system. The compartments represent regions of the body such as discrete organs, e.g., liver or kidney, or they may represent some widely distributed but physiologically similar tissue such as muscle or fat. Particular compartments generally represent macroscopic regions, but, if warranted, can also represent microscopic regions such as a single capillary with surrounding tissue. A compartment is included in a model if it represents a region of substantial uptake of the drug; if it is involved in a clearance process, such as excretion or metabolism; or if it is a site of special interest due to its toxic response to the chemical, for example, the bone marrow or a tumor. Some compartments are termed "lumped" compartments because the model assumes that the concentration of a chemical in any portion of the compartment is representative of the average concentration in the entire compartment, that is, the chemical is uniformly distributed throughout the region. Distributed models can also be formulated that take into account concentration gradients in the tissue. Dose or exposure may be initiated in the model in any compartment as an input term to that compartment. For example, an IV injection is an input into the blood compartment, dermal absorption is an input to the skin compartment, and oral or inhalation exposure could be handled by including a stomach or lung compartment in the model, respectively.

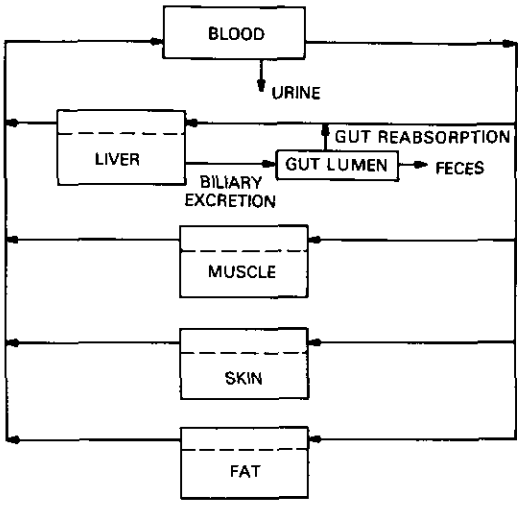

FIGURE 4. Diagram of a pharmacokinetic model for polychlorinated biphenyl in the mouse, rat, dog, and monkey.

A single, lumped compartment can be further subdivided as shown in Figure 5. Here, the various transport mechanisms are specifically illustrated. Blood or plasma flow on the arterial side carries the chemical to the capillary space of the compartment. Diffusion can occur across capillary membranes into the interstitial space, and finally transmembrane diffusion (transport) can occur to the intracellular space, which is frequently the ultimate site of action of chemical toxicity. Efferent blood leaves the compartment as the venous flow and recirculates to the blood pool.

Mathematically, the model consists of a series of mass (material) balances on each chemical species around each compartment. The material balances are in the form of differential equations that take into account blood flow, cell membrane permeability, binding, metabolism, etc. These sets of equations are solved numerically, and the resultant solutions represent simulations of the concentration of parent chemical or metabolites in all compartments as a function of time. Since it has already been postulated that the concentration of specific chemical components, such as a metabolite or a DNA adduct at a specific site of action, is a more appropriate correlate of toxicity than administered dose, a pharmacokinetic model becomes useful in estimating these specific concentrations in any tissue over time.

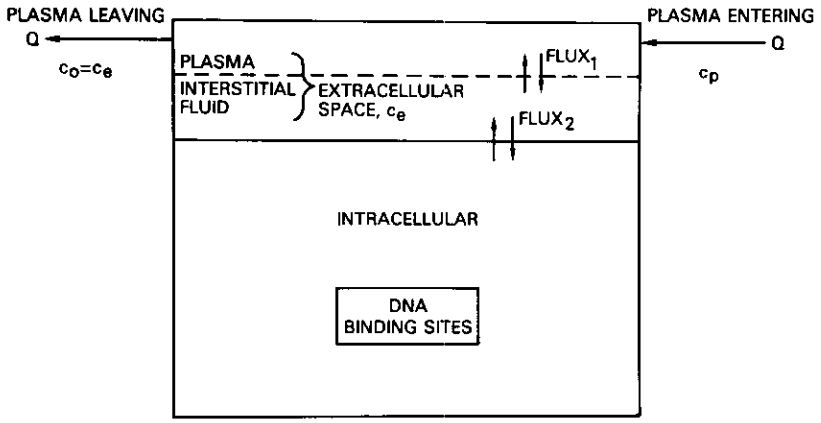

FIGURE 5. Detailed representation of a single compartment within an overall pharmacokinetic model as shown in Fig. 4.

The uses of pharmacokinetic models are several fold: They provide a means to extrapolate high dose experimental studies to low dose predictions of chemical concentration. They allow for interspecies extrapolation of exposure experiments because the models are based on physical-chemical principles that apply across species, say, mouse to man, and they can be scaled from one species to another by scaling the appropriate model parameters. They allow predictions of temporal variations in tissue concentration that might occur after exposure schedules that differ from routine bioassay studies.

Models cannot be perfect representations of the real system, but represent approximations that give us a didactic framework to gain insight into the various mechanisms that control the time history of chemicals in the body. This information may help us understand the toxic responses of some agents.

The following examples show how pharmacokinetic analysis is useful either in predicting or in interpreting toxicity studies. These examples will be presented under the heading of the category of parameter that they represent in the model.

Anatomical

Anatomical parameters relate primarily to size and body structure, e.g., body weight, organ size, or tissue space. Mammals have a remarkable geometric similarity. Figure 4 illustrates the PCB model, which, from an anatomical viewpoint, was identical for mouse, rat, dog, monkey, and man. Numerous anatomical features of mammals have been correlated in the literature according to body weight (*8*). To see how one anatomical parameter can influence chemical disposition in the body, consider Figure 6. It presents a comparison of model simulations and data for the distribution of 2,4,5,2′,4′,5′-hexachlorobiphenyl (HCB) in blood and fat of the rat (*7*). The initial model simulations were based on compartments with constant volume. According to the data, the half-life of HCB appears to be much shorter than the initial simulations. However, these experiments were conducted on young, growing rats, which, over the course of the experiment, were increasing both in total body weight and also the percent of body weight existing as adipose tissue. Fat is the primary depot for PCB distribution. After incorporating a term for increasing fat volume in the model, the simulations appeared as the solid line in the figure. What initially appeared to be washout of HCB was, in fact, a dilution effect due to the increasing fat volume. Thus, the pharmacokinetic model proved useful in identifying the storage of this highly lipid-soluble xenobiotic in fat

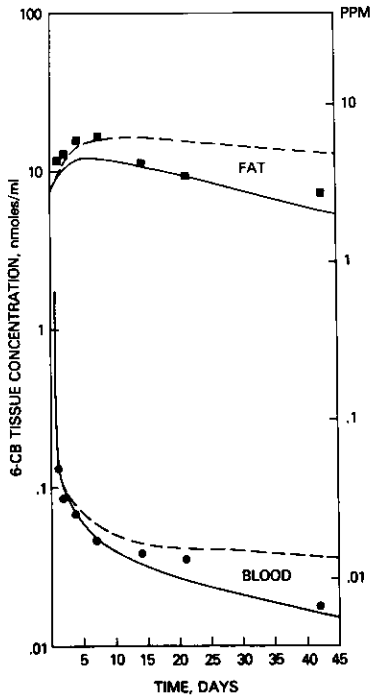

FIGURE 6. Data and model simulations for 2,4,5,2′,4′,5′-hexachlorobiphenyl distribution in blood and fat tissue in rat. Dotted line represents simulation with constant rat size; solid line represents simulation which takes into account a growing rat.

tissue, an observation with possible implications for eventual toxicity.

Physiological

Parameters that fall into the physiologic category include blood flow rate, clearance, and metabolism rates. Figure 7 illustrates how blood flow rate, a simple but often overlooked transport mechanism, can affect the distribution and tissue uptake of circulating chemicals. The figure shows three different compartments or tissues, each having a different blood perfusion rate per unit volume of tissue, as shown by the three values of Q/V. If a subject is exposed to a constant level of toxic contaminant, eventually the blood or plasma concentration of the subject will reach a steady-state level. For the example in Figure 7*A*, this concentration is arbitrarily set at 1.0. If a tissue is rapidly perfused, e.g., liver, so that the blood flow rate per unit volume of tissue is high, then the tissue concentration rises very rapidly, as illustrated by the upper curve in Figure 7*A*. If, on the other hand, the blood perfusion per unit tissue volume is low, for example, adipose tissue or skin, then the lower curve might represent that tissue's concentration over time when exposed to the same blood concentration, and we can see a slower rise in concentration. To pursue this example further, if the exposure were to cease at five time units, then one can see that the more highly perfused tissue would have about four or five times the concentration of chemical as the more slowly perfused tissue with the possible implication of a more toxic response in the former tissue. A corollary in this example is that if the blood concentration begins to decline after cessation of exposure, then the more rapidly perfused tissue will have a rapid washout of chemical and the more slowly perfused tissue would washout more slowly and have a prolonged, though lower level of chemical, in that tissue. This example, of course, assumes that the chemical is freely diffusible and not bound.

A situation similar to the washout in Figure 7*A* is represented in Figure 7*B*, which shows the concentration in three tissues with different perfusion rates after exposure to an acute, single bolus of chemical in the blood that eventually is cleared. The rapidly perfused tissue achieves a high peak concentration but washes out rapidly; the slowly perfused tissue has a much lower peak concentration, but it persists for a longer time. The question of which situation would be more toxic has no clear-cut answer. It would depend on the mechanism of the toxicity and on the toxic agent. For compounds whose evoked response is dependent on peak tissue concentration, then the upper curve is more toxic. For example, the lowering of blood pressure by minoxidil (*9*) or the degree of paralysis from tubocurrarine (*9*) are determined by magnitudes of blood or tissue levels. However, excessive peak levels could cause seizure or death. If, on the other hand, the chemical was cytotoxic during certain phases of cell replication (i.e., cell-cycle specific), a toxic response would be evoked only if a sufficient tissue concentration were maintained long enough to cover the sensitive cell cycle time. In such a

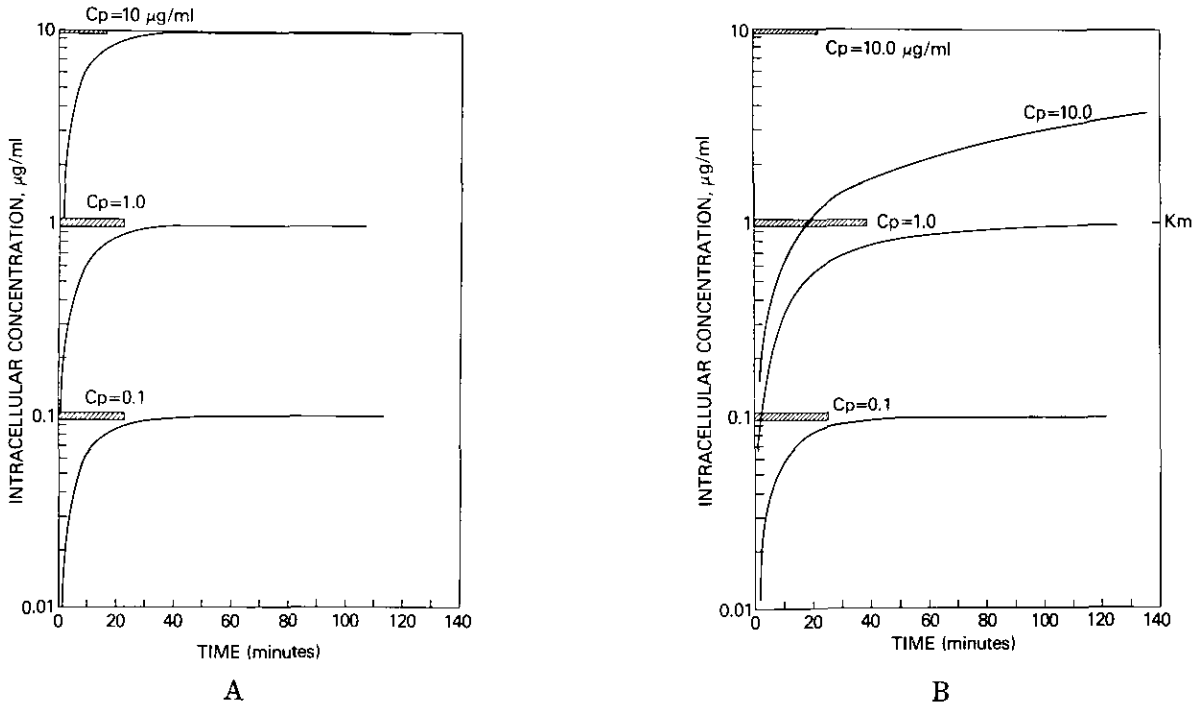

FIGURE 7. Computer simulation of the concentration of an administered chemical in several hypothetical compartments each with a different ratio of blood perfusion to tissue volume, Q/V. (*A*) Exposure to a constant blood concentration; (*B*) exposure to a declining blood concentration after a single acute exposure.

case, the lower curve in Figure 7*B* might prove to be a more toxic time course for such a chemical. Examples of this effect have been described in the literature for chemotherapeutic agents (*10–13*), although the same principles can apply to certain toxins.

It is important to recognize that even simple considerations, like tissue blood flow, though a pharmacokinetic phenomena, can have implications on toxic response to a chemical and should be taken into account.

Clearance

Clearance relates to mechanisms of removal of chemicals from the body by such systems as the kidney via urinary elimination, and liver and gut via biliary and fecal elimination. Obviously, the ability to remove a toxic chemical from the body influences the degree and duration of toxic response. Clearance, as a physiologic model parameter, provides a useful format in pharmacokinetic analysis for interspecies extrapolation. Examples exist where certain clearance values follow an empirical correlation among several species so that predictions in man can be made for the rate of removal of a chemical based on animal experiments using a pharmacokinetic model (*14–16*). Figure 8 shows an example of such a correlation for the kidney clearance of the anticancer drug cytosine arabinoside (ARA-C) as a function of body weight (*17*). Represented in the figure are data collected from mouse, dog, monkey, and man. The correlation with body weight is quite good. Human clearance values for particular environmental contaminants may be estimated by similar extrapolation procedures and used in pharmacokinetic models to predict human concentrations.

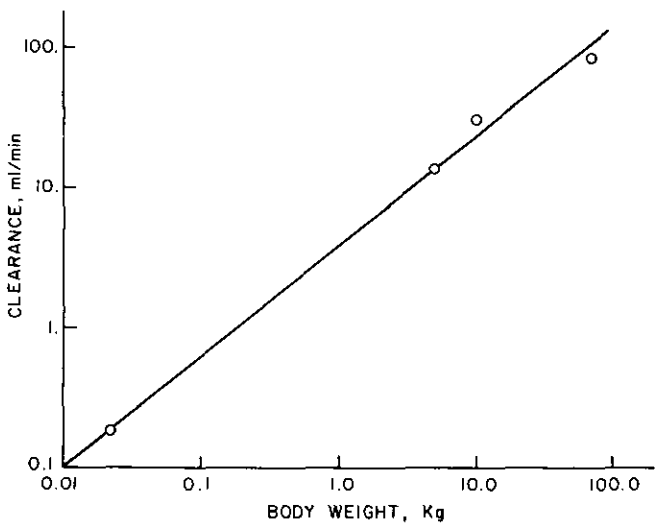

FIGURE 8. A correlation for kidney clearance of cytosine arabinoside versus body weight of several mammalian species. Slope of the line is approximately 0.8. (O) Data points from left to right are from mouse, dog, monkey, and human, respectively.

Metabolism

Another physiological parameter that is extremely significant in the consideration of toxicity is metabolism. In one case, metabolism may be responsible for the formation of a reactive species *in vivo* and would contribute to toxicity, whereas in another case, metabolism may be the essential step in a detoxification process either by reducing the toxic form to an innocuous form, or by conjugating the toxic species prior to its eventual removal from the body. Often, metabolic processes in the body are enzymatic and follow Michaelis-Menten kinetics. As such, the rate of reaction can be a linear function of concentration at low doses and nonlinear at high doses. The consequences of extrapolating high dose data to low dose response predictions without accounting for nonlinear mechanisms has been described earlier in this paper with references to Figures 2 and 3.

Aside from dose extrapolation, interspecies extrapolation of metabolic data is relevant to toxicity studies, as most predictions for human response are based on animal data. Improper consideration of metabolic differences among species, both qualitative and quantitative, can lead to erroneous conclusions about toxicity. Unfortunately, metabolism rates are the most confounding parameters to extrapolate from species to species. An example of the unpredictability of metabolism rates across species is evident from previous pharmacokinetic analysis of PCBs in mouse, rat, dog, and monkey (*18*). Table 1 shows the metabolism rates reported in terms of clearance values (mL/min) for these species for three congeners of PCB. The upper half of the table shows that the metabolism rates increase monotonically with increasing size of the animal as one might expect. This is true for each of the three congeners studied. If, however, an intrinsic metabolic rate is calculated as milliliters per minute per kilogram of body weight, a different pattern emerges. The mouse and rat have similar intrinsic metabolic rate constants for each congener, whereas the money has lower rate constants, and the dog, higher rate constants. These metabolism constants are reflected in the half-lives of the PCBs in these animal species, since metabolism and subsequent conjugation are generally considered to be a prerequisite to elimination of PCBs by bile and feces. Under these circumstances, it would be difficult to make *a priori* predictions of which species would serve as the best animal model

Table 1. Metabolic clearance of PCBs in several species.

PCB	Mouse	Rat	Monkey	Dog
K_m, mL/min				
4,4′-DCB	0.37	2.0	7.0	470
2,4,5,2′,4′,5′-HCB	0.01	0.045	0.67	16.0
2,3,6,2′,3′,6′-HCB	N/A	5.0	15.0	183
K_m, per kg body weight, mL/min/kg				
4,4-DCB	9.7	8.0	1.4	39
2,4,5,2′,4′,5′-HCB	0.25	0.18	0.13	1.33
2,3,6,2′,3′,6′-HCB	N/A	20	3.0	15.2

of human response to PCB exposure. Here again, however, a pharmacokinetic model can be very useful, because it can incorporate a recently advanced method known as *in vitro-in vivo* correlation. The method uses *in vitro* systems, such as tissue homogenates, microsomal preparations, and even isolated, perfused organs from each animal species to estimate metabolic rate constants for that species (*19–23*). The reactions are frequently enzymatic. Comparable tissues or preparations are often available from human subjects, for example, from biopsy specimens. The *in vitro* reaction rate constants determined from all species, including humans, can be compared, and when converted to a proper basis, can be incorporated as a metabolism parameter in the appropriate compartment in the physiological pharmacokinetic model for prediction of concentrations. Such *in vitro-in vivo* correlation schemes, which have already been reported in the literature, show great promise toward improving predictability in humans when *in vivo* metabolic data are not otherwise available.

Thermodynamic

Thermodynamic parameters relate primarily to terms that describe purely physical interactions of exogenous chemical with biological tissues and fluids in the form of equilibrium distributions such as protein binding and tissue partitioning. Their values determine the total concentration of chemical in a tissue relative to blood. In contrast to metabolism values, these parameters are quite similar from species to species (*15,16*). Figure 9 helps to illustrate this point using the example of 2,4,5,2′,4′,5′-hexachlorobiphenyl (HCB) distribution in several tissues of the rat. The fat or adipose tissue has the highest concentration of HCB, skin is next, and muscle tissue is the lowest. This order of concentration reflects the high degree of lipid solubility of PCB, and this thermodynamic property is remarkably similar from species to species, as shown by a comparison of partitioning coefficients for mouse, rat, dog, and monkey (*18*). This greatly enhances interspecies extrapolation, including predictions of levels in humans. Also, *in vitro-in vivo* correlations are possible for thermodynamic parameters as well, for example, by cross-correlating lipid content or specific binding protein levels from tissues of different species (*24–26*). These thermodynamic parameters are easily incorporated into the pharmacokinetic model.

Transport

Another concept to consider in risk assessment analysis is the time-dependent concentration of a toxic agent at the intracellular site of action. This process is represented by the biological model in Figure 2. In some cases, the time course of uptake of a chemical by a tissue is limited by blood flow rate to that tissue, as described previously. However, in other instances, the rate of tissue uptake may be controlled by the rate of transport across cell membranes to the intracellular compartment. The controlling factor depends on the relative values of blood flow rate and membrane permeability of each tissue. If the former is much smaller, then we refer to this as "flow-limited" uptake, if the latter is much smaller, then "membrane-limited" uptake predominates. The limiting factor can vary from tissue to tissue or even from chemical to chemical in a given tissue.

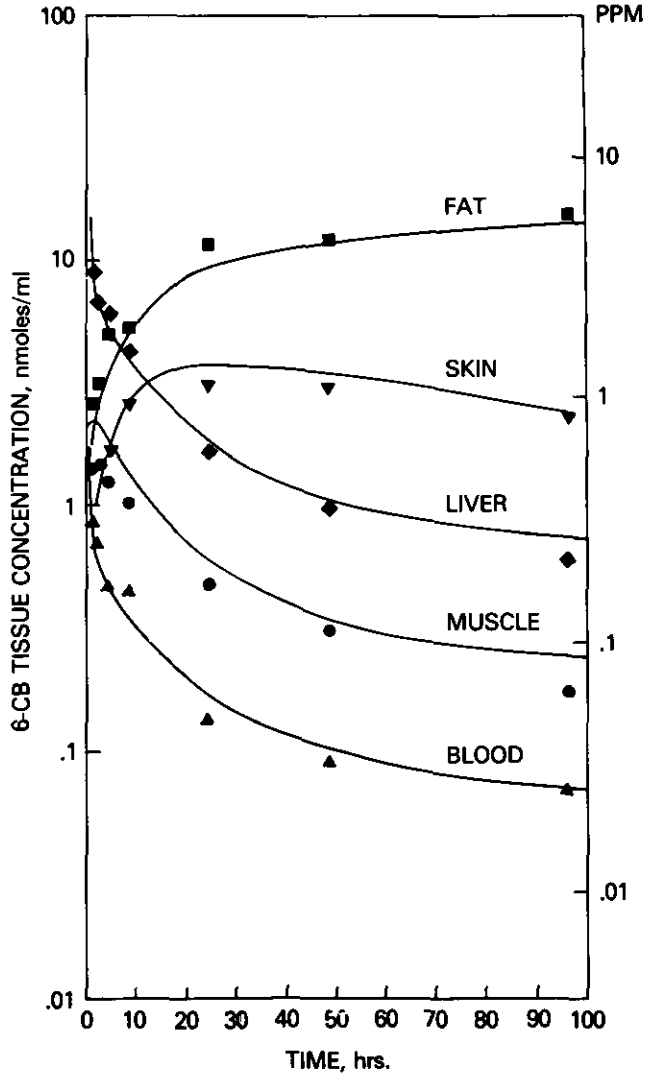

FIGURE 9. The concentration-time course of 2,4,5,2′,4′,5′-hexachlorobiphenyl in the rat for several tissues. This illustration reflects tissue-specific partitioning of 6-CB according to a thermodynamic equilibrium that is predictable across several species such as mouse, rat, dog, and monkey.

For membrane transport, two mechanisms are possible, one in which the transmembrane transport occurs primarily by passive diffusion across the cell membrane; the other, in which facilitated or carrier-mediated transport occurs across the cell membrane, whereby the diffusing chemical first binds to a carrier protein on the cell membrane surface and then the whole complex is transported through the membrane to the intracellular

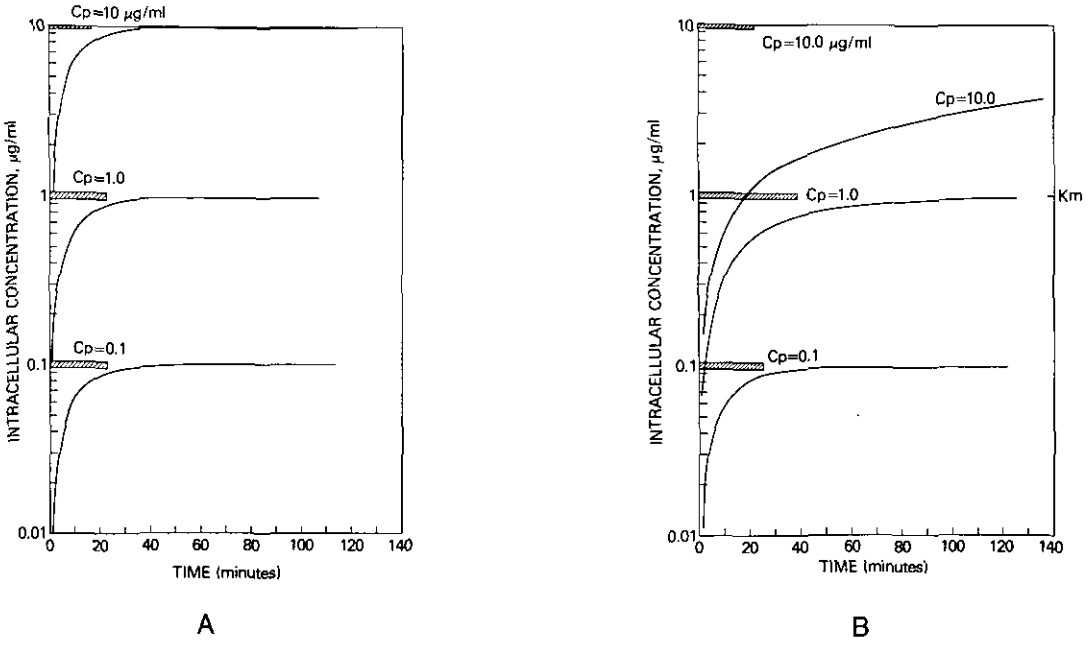

FIGURE 10. A computer simulation showing the intracellular concentration of a chemical as a result of transport across cell membranes. (*A*) A saturable transport mechanism after exposure to several blood concentrations, C_p; (*B*) a linear, nonsaturable transport mechanism after exposure to the same blood concentrations as in (*A*).

compartment. The former situation is usually a linear process as a function of concentration; the latter can be saturable and nonlinear.

Examples of each of these situations follow. Figure 10 illustrates a computer simulation of the intracellular concentrations of some exogenous chemical under three different exposure conditions where the blood or plasma concentration, C_p, increases by 10-fold in each case. The model used to generate the curves in Figure 10*A* represent a linear mechanism for membrane transport, such as simple diffusion proportional to C_p. The intracellular concentrations are seen to rise proportionately with the exposed dose. On the other hand, the illustrations in Figure 10*B* depict computer simulations of a saturable transport mechanism. In this example, the saturation of the carrier-mechanism begins to occur at a plasma concentration near $C_p = 1.0$. This happens to be the value of the dissociation constant of the substrate-carrier complex, $K_m = 1.0$. At low doses, when the plasma concentrations are below $C_p = 1.0$, the transport appears to be linear, as intracellular concentrations are nearly proportional to C_p as in Figure 10*A*. However, at higher doses, when C_p exceeds 1.0, the intracellular concentration is no longer proportional to dose for the same time of exposure. Longer exposure times will eventually allow intracellular concentrations to rise up to the blood levels.

These examples provide further evidence of the importance of pharmacokinetic analysis in interpreting toxicity assays. According to these examples, situations could exist where knowledge of the ambient exposure levels or even blood levels alone is not sufficient to correlate with possible toxic response because intracellular concentrations may not be proportional to varying exposure levels. Likewise, the temporal nature of the exposure may be important in determining actual tissue uptake at a site of action. The pharmacokinetic model is capable of incorporating this relevant information.

In summary, then, pharmacokinetic analysis is an important asset, if not an essential ingredient in interpreting host response to toxic chemicals. Pharmacokinetic models are useful tools for describing and predicting pharmacokinetic events, especially when they incorporate relevant anatomical and physiological parameters similar to those described here. The model is an excellent didactic device that forces us to formulate our hypothesis in an organized format. The model allows us to extrapolate from high dose to low dose; extrapolate from species to species; and account for temporal variations in dose. All of these factors are certainly important considerations in risk assessment.

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